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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,814	03/26/2001	Michael Jeffers	15966-557CIP2 (Cura-57CIP	7821

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EXAMINER
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ART UNIT	PAPER NUMBER
1647	18

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,814	JEFFERS ET AL.	
	Examin r	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the c ver sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20,33,43,48,66 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *18-20,33,43,48,66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to the amendment and remarks filed on 4/21/03 in Paper No: 17. Applicant has cancelled claims 1-17, 21-32, 34-42, 44-47 and 49-65. Applicant has added claims 66 and 67. Thus, claims 18, 19, 20, 33, 43, 48, 66 and 67 are pending.

2. The change of title is acknowledged.

3. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record, which is not expressly repeated in this action, has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed 21 April 2003 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 101

6. Claims 18, 19, 20, 33, 43, 48, and 66-67 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility for the reasons of record as applied to claims 18, 19, 20, 33, 43 and 48.

Applicant's arguments filed 21 April 2003 have been fully considered but are not deemed to be persuasive. Applicant argues that the specification provides specific examples of utility. These arguments are not persuasive for the following reasons. (1) Amino acid sequence identity to other FGF proteins is not sufficient for establishing utility because structural analogy to a known compound with a known activity and utility

is not sufficient evidence of utility for the claimed compound (see *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966)). (2) Conservation of an FGF family domain does not provide a specific, substantial and credible utility for the claimed compound because not all of the FGF proteins of the family have the same utility. In other words, conservation of structure does not result in conservation of function and this conclusion was supported by the Galzie et al. reference in the previous Office action. (3) The presence of an FGF internal hydrophobic transport domain does not provide a specific, substantial and credible utility for the claimed protein, although it is suggestive that the claimed protein is a new member of the FGF family. (4) The characteristic of binding heparin by the claimed protein does not establish a specific, substantial and credible utility, absent evidence to the contrary. (5)-(6) The biological activity of the claimed polypeptide in Examples 9-11 was noted in the previous Office action. The issue with the disclosed biological activity is that the instant specification teaches that administration of the polypeptide stimulates proliferation of fibroblasts in culture, but these cells also lose contact inhibition, meaning that the cells take on a transformed phenotype. The instant specification does not demonstrate an *in vivo* activity of the claimed polypeptide because Example 11 is directed to tumor formation by ectopic FGF-CX-transfected NIH 3T3 cells, which is not exogenous administration of the polypeptide *in vivo*. The activity of a cell line transfected with a protein is not predictive of the administration of the same polypeptide to an animal; one of ordinary skill in the art would not necessarily expect to obtain the same results and therefore, the same biological activity. Additionally, the instant specification does not teach a specific,

substantial and credible utility for a protein which stimulates fibroblasts in culture, but also transforms them so that they lose contact inhibition. There is no "real world" use for such a protein with this activity, absent evidence to the contrary.

Applicant argues at pages 7-10 of the response that the claimed invention is an FGF protein and that there is well-established utility for FGF proteins. This argument is not persuasive for the reasons of record in that there is no well-established utility for the FGF family because the biological activities for the members of the family are diverse and not all the members share a common function. This diversity was evidenced by Galzie et al., cited in the previous Office action. Galzie et al., stated that the complexity of the FGF family and the FGF-induced responses is reflected in the diversity and redundancy of the FGF receptors. Thus, it appears that even with substantial homology among FGF family members there is still considerable diversity in its biological functions. The fact that protein of the instant invention has 100% identity with human FGF-20 is not in dispute. However, this is a post filing information and clearly Applicants were not in possession of this at the time the application was filed.

Applicant also asserts that the claimed protein stimulates NIH 3T3 cells, and therefore, has been shown to stimulate cell growth and proliferation. However, this is not a complete characterization of the biological activity demonstrated for the claimed protein. The protein stimulates NIH 3T3 cells and also causes them to lose contact inhibition. This latter activity is not separable from the ability to stimulate proliferation, and the instant specification does not teach a utility for a protein that transforms cells as well as inducing proliferation. The specification asserts that the claimed invention could

be used in a method of diagnosing, treating, preventing, or delaying a tissue proliferation-associated disorder, such as "tumors, restenosis, psoriasis, Dupuytren's contracture, diabetic complications, Kaposi sarcoma, and rheumatoid arthritis" (see page 6, lines 3-7 of the specification), in a method of "treating a pathological state in a mammal" by administering the polypeptide (see page 5, line 6), in a method of "promoting growth of cells in a subject" wherein the cells are "in the vicinity of a wound, cells in the vascular system, cells involved in hematopoiesis, cells involved in erythropoiesis, cells in the lining of the gastrointestinal tract, and cells in hair follicles" (see page 5, lines 15-21), in "methods of diagnosing the presence or amounts of these compositions, in screening for and identifying therapeutic agents related to FGF-CX-associated pathologies, and in methods of treatment of various kinds of malignancy" (see sentence spanning pages 17-18), for use in screening assays, detection assays, predictive medicine, and methods of treatment (see sentence spanning pages 67-68), for stimulation of fibroblasts for use in wound healing (see page 76, lines 29-30), for stimulation of hematopoietic cells, immune system cells, and vascular smooth muscle cells, as well as for treating bone fractures and osteoporosis (see page 77, lines 1-3), diagnosis of cerebral tumors (page 77, lines 3-4), and for treatment of cancer (page 77, lines 9-13). However, neither the specification nor the prior art demonstrates a causal correlation or nexus of the claimed polypeptide with any of the conditions or disorders contemplated by the instant specification, therefore, there is no evidence of record that would provide for a method of treating/diagnosing any of the listed conditions or disorders.

In addition, one of ordinary skill in the art would not believe the assertions to be credible for treatment of the above listed conditions in light of the evidence in the specification that the claimed invention transforms fibroblast cells in addition to stimulating proliferation.

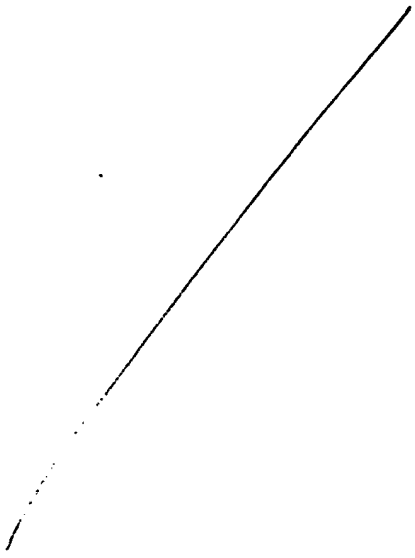
Applicant argues on page 8 of the response that the instant specification makes multiple specific assertions of utility for the claimed utility. It is asserted that the polypeptide of the instant invention stimulates epithelial cells, glial cells and cells found in the lining of the gastrointestinal tract. The asserted use of "stimulating/growth of cells in the lining of the gastrointestinal tract in order to treat intestinal inflammation and ulcers" is not specifically recited in the specification as filed because it is but one in a list of unrelated uses (see pages 78 and 79). In fact, the Applicant also asserts that the polypeptide of instant invention also may be used to stimulate new cell growth in neurological disorders including, Alzheimer's disease. In addition, it is further asserted that antagonistic treatments may be administered in which an antibody specifically binding the FGF-CX-like proteins of the invention would abrogate the specific growth-inducing effects of the proteins. Thus, it is suggested that such antibodies may be useful, for example, in the treatment of proliferative disorders including various tumors and benign hyperplasias (page 79, lines 2-3). Furthermore, the Jefferes et al. (Gastroenterology, 2002) and the FDA approval (2003) for the treatment of oral mucositis are post filing evidence of the use of the instant invention. Thus, the use of FGF-CX for the treatment of ulcers was not substantial at the time it was filed.

Applicant argues on page 10 of the response that Galzie et al. does not support a case for lack of utility. This argument is not persuasive. Galzie et al. was cited to demonstrate that there is no well-established utility for the FGF family of proteins because each of the members has distinct and diverse activities even though structural similarity is present.

Applicant argues that the FGF-CX antibodies can be used diagnosing proliferative disorders. This argument is not persuasive because there was no evidence of correlation or nexus between the claimed invention and any disorder at the time of filing. Furthermore, Applicants recitation of the use of the antibody in therapeutics not specifically recited in the specification as filed because it is but one in a list of unrelated use (see pages 78 and 79). Applicant points to Kurokawa et al. (5,571,815) to indicate anti-tumor activity of the antibody. However, Applicant in the specification recites several potential uses and post filing provides evidence for one such use. To employ the instant invention in any of the disclosed methods would clearly be using it as the object of further research which has been determined by the courts to be a utility which, alone, does not support patentability. The instant specification provides data on expression of the claimed protein, indicating that it is expressed in normal cerebellum, as well as in several human tumor cell lines without being expressed in corresponding normal tissues. The specification provides a chromosomal location for the FGF-CX and "[e]xpression of heterologous FGF-CX in NIH 3T3 cells is found to induce their transformation and tumorigenicity" (see page 17, lines 15-16). However, these disclosed properties of the claimed protein, expression pattern and ability to transform

fibroblast cells in culture does not provide a specific, substantial and credible utility for the claimed polypeptides. Expression of the claimed polypeptide in cancer tissue does not establish a nexus between the claimed protein and cancer growth. Expression of the claimed polypeptide could just as likely be a result of the cancer, and not a causative agent, therefore one of ordinary skill in the art could not target the claimed polypeptide for treatment of the cancer. The instant specification fails to teach that the claimed polypeptide is diagnostic for any specific cancer, as it is found in normal and diseased tissue.

Since the instant specification does not disclose a credible "real world" use for the claimed invention, it is incomplete and, therefore, does not meet the requirements of 35 U.S.C. §101 as being useful.



Claim Rejections - 35 USC § 112

7. Rejection of claims18, 19, 20, 33, 43, 48, and 66-67 under 35 U.S.C. §112, first paragraph, as failing to adequately teach how to use the instant invention is maintained for those reasons given above in paragraph 6, with regard to the rejection of these claims under 35 U.S.C. §101.

8. Rejection of claim 18 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

Claim 18 recites the limitations of "retains the conserved amino acids of the FGF family motif located at residues 125, 127, 129, 136, 137, 141 and 148, and retains the hydrophobic transport domain between residues 92-120, wherein the residues are numbered with respect to SEQ ID NO: 2". There is no basis in the instant specification for these limitations, contrary to Applicant's assertion. A careful review of the specification as originally filed, including pages 26-27, Examples 9-10 and Figures 16-18, failed to reveal these limitations or the inventive concept of these limitations. Therefore, the claim is directed to subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. Claims 66-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 66 and 67 are directed to polypeptides having a post-translational modification other than a proteolytic cleavage, and specifically phosphorylation or N-myristoylation. However, the instant specification fails to provide a written description of that subject matter which is being claimed.

There is no disclosure of any post-translational modification of the polypeptide of SEQ ID NO: 2. Additionally, there is no disclosure of phosphorylation or N-myristoylation, and it is not clear if the claimed polypeptide would even be able to undergo these post-translational modifications (i.e. proper amino acid sequence for such to occur or expression by a host which would perform these modifications, etc.). Namely the sequences identified on exhibit 4 were not present in the specification as it was originally filed to indicate Applicant had possession of the invention. Contrary to the assertion made by the Applicant, mature form of the polypeptide cannot be reasonably predicted because there is no evidence provided with respect to *in vivo* proteolytic cleavage sites and the processing of it. The claims are directed to proteins with modifications which may or may not occur, the structure of which cannot be determined or predicted from full-length amino acid sequence, with no evidence of isolation or conception of the structure thereof, therefore, the specification does not provide an adequate written description of the claimed proteins, and thus the claimed invention was

not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

With the exception of very particular amino acid sequences, which are disclosed in the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide molecules and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of protein expression. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific molecular structure is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) The instant claims are directed to a structure,

which could be made, but for which, there is no written description. As in Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class because the specification provided only the bovine sequence. In the instant situation, the specification only provides the full length protein, but fails to provide a description of the "broad class" of polypeptides having post-translational modifications regardless of whether they could be made or isolated.

10. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Although, Applicant asserts that there is adequate description in the specification to convey that they contemplated and possessed such various polypeptides at the time of filing. The instant specification teaches a single example of a polypeptide (SEQ ID NO: 2), and fails to teach any other polypeptides having at least 85% identity, or variants of SEQ ID NO: 2. In addition, Applicant points to Table 2 to show possible changes in the polypeptide. However, there is no description or guidance to generate the variants.

Claim 18 includes embodiments of polypeptides having at least 85% sequence identity to SEQ ID NO: 2. The instant specification fails to describe the various polypeptides which meet these limitations of the claims. In making a determination of whether the application complies with the written description requirement of 35 U.S.C.

112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of a protein which has the amino acid sequence of SEQ ID NO: 2. The subject matter which is claimed is described above. First, a determination of the level of predictability in the art must be made in that whether the level of skill in the art leads to a predictability of structure; and/or whether teachings in the application or prior art lead to a predictability of structure. The claims are directed to polypeptide which have sequence identity or to variants of the disclosed polypeptide of SEQ ID NO: 2. First, the claims are not limited to any particular polypeptide, in that the claims are also directed to variant forms thereof. The specification only describes a single polypeptide and fails to teach or describe any other molecules which meet the structural limitations of the claims. The breadth of the claims is such that the claims encompass polypeptides from other species, related polypeptides and variants which have yet to be described. There is a lack of guidance or teaching regarding structure and function of the polypeptide because there is only a single example of a polypeptide provided in the specification and because there is no guidance found in the prior art for this specific polypeptide.

Next in making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, each claimed species and genus must be evaluated to determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed. With this regard, the instant application fails to provide a written description of the species or the genus which are encompassed by the

instant claims except for the polypeptide of SEQ ID NO: 2. The specification does not provide a complete structure of those molecules which have at least 85% sequence identity to SEQ ID NO: 2, or to variants of the disclosed polypeptide of SEQ ID NO: 2. The claims also fail to recite other relevant identifying characteristics (physical and/or chemical and/or functional characteristics coupled with a known or disclosed correlation between function and structure) sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. The specification fails to provide a representative number of species for the claimed genus because the specification teaches a single embodiment. Therefore, the claims are directed subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and thus the rejection is maintained.

11. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendments do not obviate the rejection of record in Paper No: 14, page 14. Again the specification does not teach an antibody that is capable of regulating the FGF-CX expression. Even if an antibody to the peptide was isolated it is unclear if this antibody will be capable of regulating the polypeptide of the invention. It is also

unclear what is the pathology Applicant intends to treat by regulating the expression of the FGF-CX polypeptide. It appears that the Applicant is attempting to define this antibody functionally. The claims as written, however, encompass an antibody which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claim 33. Thus, it does not appear that the inventors were in possession of the invention and the rejection is maintained.

12. Claim 33 is rejected as vague and indefinite in the recitation of the phrase "treatment of a pathology and functional growth factor like properties". It is unclear what pathology is treated or what growth factor like properties are altered by the antibody of the instant invention.

13. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

15. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JSS

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud